Critical Challenges and Opportunities for Probiotic Innovators

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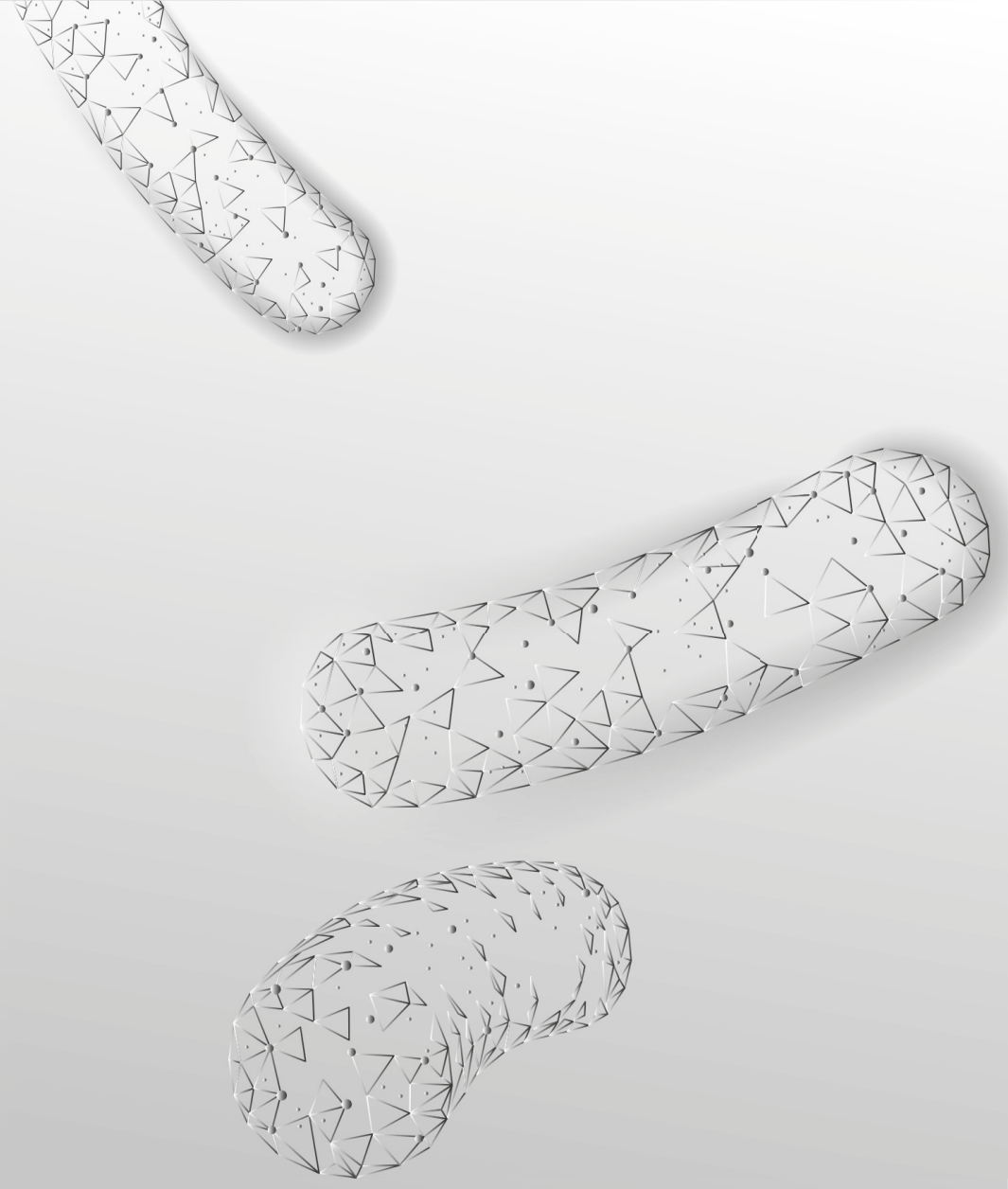

CHAPTER 2.

The Nagoya Protocol on Access to Genetic Resources and Benefit Sharing: *Best practices for users of Lactic Acid Bacteria*

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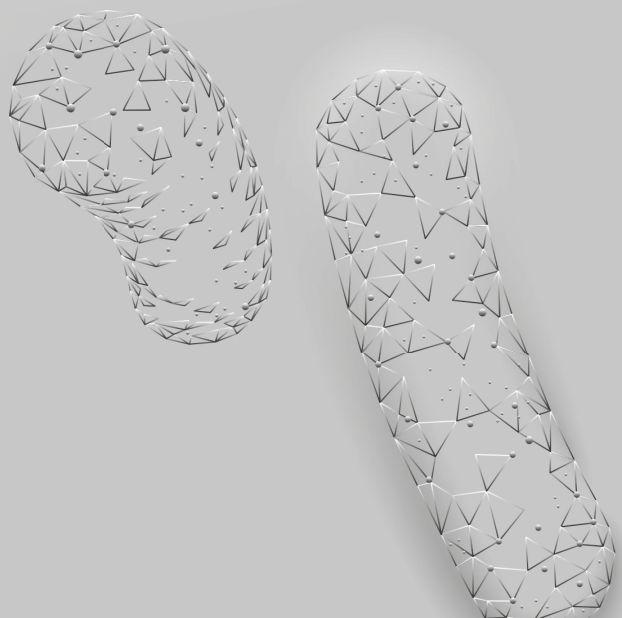

2.1 ABSTRACT:

Lactic Acid Bacteria (LAB) have great potential to advance human health and therefore see vast applications in pharmaceutical and food industries. Global collaboration and open innovation, where LAB are shared and their genomes are sequenced, are essential for the study and discovery of new underlying probiotic effects. However, recent efforts of the Nagoya Protocol (NP) to the Convention on Biological Diversity have created legal barriers on the access and use of genetic resources (such as LAB). This is to promote conservation and sustainable use of biodiversity, by protecting the rights of local communities and their traditional knowledge. While these objectives are positively supported, industry users of LAB indicate that the legislative burden of the NP can be disproportionally high and therefore hampers knowledge valorization and R&D activities aimed at probiotic innovation. To this end, we set out to explore the implications of the NP for commercial users of LAB by delineating best practice solutions for the probiotic industry. We also review the innovation barriers associated with the default implementation of the NP and express the need for a multilateral system in which a set of standardized rules for efficient access to LAB are agreed between ratifying parties.

Key words: Nagoya Protocol, Probiotics, Lactic Acid Bacteria, Access and Benefit Sharing legislation, Convention on Biological Diversity

2.2 INTRODUCTION

Genetic resources (GRs) are genetic material of actual or potential value which contain functional units of heredity and can be used in crop protection, food and drug development, the production of specialized chemicals, or in industrial processing (CBD, 2010). GRs have therefore played a fundamental role throughout human civilization and were fostered through the anthropogenic spread of animals, plants and microbes globally (Chiarolla et al., 2010). Within this development, the propagation and cultivation of Lactic Acid Bacteria (LAB) significantly improved the stability, quality and organoleptic properties of our food supply as they were widely used in fermentation processing (Gibbons et al., 2015). These microorganisms also played a vital role in the advancement of human health due to their health promoting properties (Flach et al., 2018a; Kerry et al., 2018; Khalesi et al., 2018). It is reported that LAB may promote innate and adaptive immune systems, protect against infections, and reduce (antibiotic associated) diarrhea (among a wide range of other health benefits (Flach et al., 2018a; Kerry et al.,2018)). In contemporary culture, these bacteria therefore see vast applications in pharmaceutical and food industries and are commonly referred to as probiotics (although other microbes may also be considered a probiotic). The global probiotic market was estimated at 49 billion dollars in 2018 and is expected to reach 69 billion dollars by 2023 (Caselli et al., 2013; MarketsandMarkets., 2018), indicating that LAB are widely used by consumers and industry. Provided this widespread use of LAB in conventional (probiotic) products and their potential to advance human health, it is crucial that global collaboration and open innovation (in which LAB are shared and their genomes are sequenced) are stimulated to foster the study and discovery of new underlying probiotic effects that may alleviate society's unmet medical needs (van den Nieuwboer et al., 2016a).

The exchange of GRs (such as LAB) historically occurred in an informal way between laboratories, culture banks and researchers worldwide (Dedeurwaerdere et al., 2009). This unconstrained access and use of GRs, however, led to the reported exploitation of developing countries and their traditional knowledge through the practice of 'biopiracy', meaning that commercial entities (mostly from developed countries) were accused of accessing and utilizing a wide array of indigenous GRs and filing restrictive patents that did not acknowledge the country of origin either financially or otherwise (Buck & Hamilton, 2011). The Convention on Biological Diversity (CBD) therefore assumed a leading role on regulating the use and exchange of GRs in an international context, by taking into consideration the requests

of developing countries for fair and equitable sharing of benefits arising from the utilization of their GRs. As a result, the Nagoya Protocol (NP) on Access and Benefit Sharing (ABS) was developed in which certificates and contractual obligations became mandatory to substantiate legal access and use of GRs originating from countries that ratified the Protocol (CBD, 2019a) (Box 2.1).

While the underlying principles of the CBD are broadly recognized and supported, users of LAB indicate that the regulatory requirements to access and utilize GRs under the NP are at odds with prevailing open sharing practices and can be disproportionally high or unattainable (Johansen et al., 2017). Consequently, these users may be tempted to source GRs from countries that choose not to exert their sovereignty rights (and therefore do not require access and benefit sharing), leaving many potentially beneficial LAB underutilized. This hampers (probiotic) knowledge valorization (van den Nieuwboer et al., 2016b) and directly goes against the objectives of the CBD to conserve biological diversity and promote sustainable use of its components globally. The Lactic Acid Bacteria Industrial Platform therefore formulated recommendations to ease the regulatory burden of the NP and expressed the need for 'best practice solutions' from industry and academia (Johansen et al., 2017). To address this need, we set out to explore the implications of the NP for commercial users of LAB, by delineating best practice solutions for the probiotic industry on the fair access and use of LAB in accordance with the current ABS framework and associated legislation.

Nagoya Protocol

The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity was adopted at the tenth meeting of the Conference of the Parties, in Nagoya, Japan on 29 October 2010 (CBD 2019a). The NP entered into force on 12 October 2014 (CBD, 2019a), and so far, more than 100 countries have ratified the Protocol. These include countries from Asia, Africa and Latin America, as well as China, India, Norway, Switzerland, Japan, and the European Union (EU) as a whole (CBD, 2019b). The US has not ratified the Protocol, and hence is not a party to it. The objective of the NP is to promote transparency on the management of GRs by providing a legal framework that supports the implementation of the CBD's third objective: the fair and equitable sharing of benefits arising from the utilization of GRs (CBD, 2019a). This framework addresses two important phases on the management of GRs: access and use. The idea is to preserve the rights from the providers of GRs through the transfer of relevant technologies and appropriate funding, thereby contributing to the conservation of biological diversity and the sustainable use of its components globally (CBD, 2011).

Box 2.1 History and scope of the Nagoya Protocol

2.3 METHODOLOGY

To attain the objectives of the present study, a decision framework was developed (Fig. 2.1) in which ABS obligations are depicted in a stepwise and chronological order. A literature search was conducted to identify existing guidance documents on compliance with the NP. The resulting framework was based on the descriptions provided by: (1) the Netherlands ABS Focal Point (based on EU Regulations on compliance with the NP (EU 511/2014)) (NFP The Netherlands, 2018); (2) the TRUST World Federation for Culture Collections' systems (TRansparent Users-friendly System of Transfer (WFCC, 2018)); and (3) the Consortium of European Taxonomic Facilities' Code of Conduct and Best Practices on ABS (CETAF, 2017). These reference systems address access and use of GRs in an international context but are primarily focused on the regulations and interpretations within the EU. In the present study, we address the NP in a broader global context and focus on the perspective of potential users from the probiotic industry.

2.4 BEST PRACTICES

To foster the central objectives of the CBD and NP, we first delineate the steps to access and utilize GRs in accordance with the current ABS framework and associated legislation. Key considerations are summarized in the NP decision framework (Fig. 2.1) and are subsequently contextualized to users of LAB from the probiotic industry (section 2.4.1-2.4.3). By following the steps outlined in this framework, (probiotic) companies can reaffirm that they have conducted the appropriate due diligence for the legal access and use of GRs regarding the NP, and the reporting requirements to national checkpoints, where necessary (EU Regulation 511/2014 and Implementing Regulation EU 2015/1866).

2.4.1 Access to Genetic Resources

The first step that must be considered for compliance with the NP is whether a company's research and development activities involve (access to) GRs. The CBD defines GRs as: "*genetic material of actual or potential value"*, where genetic material is considered to be *"any material of plant, animal, microbial or other origin containing functional units of heredity"* (CBD, 1992; European Commission, 2016). In this sense, LAB and other probiotic microorganisms clearly meet the definition of GR as applied by the CBD and NP (Schrezenmeir & de Vrese, 2011). Nevertheless,

there is a lack of consensus on whether genetic sequence data and organisms from the human microbiome should also be considered a GR under this definition (see section 2.5.2).

2.4.2 Scope of the Nagoya Protocol

It should then be assessed whether the GR is accessed after 12 October 2014 (when the NP entered into force) and whether the provider country has ratified the Protocol (as can be seen on the ABS Clearing House on the CBD website). If these conditions are not met, GRs are considered outside the scope and are therefore not covered by the NP. The Protocol´s scope is furthermore limited to "utilization" of GRs, where utilization is defined as *"to conduct research and development on the genetic and/or biochemical composition of genetic resources, including through the application of biotechnology"* (CBD, 2011). The use of LAB in (industrial) processes, such as bioprocessing, adaption or *in vitro* testing evidently are considered utilization. However, what exactly is entailed by R&D is not always clearly defined and may therefore be subject of debate (section 2.5.2).

2.4.3 Origin of the material

Subsequently, the origin of the material should be considered. For GRs that are obtained *in situ* (in its natural surrounding or habitat), users should contact the Competent National Authorities in the provider country directly to establish terms for legal access and use of the material (section 2.4.4). If GRs are obtained *ex situ,* for instance from gene banks or culture collections, certificates and agreements on the legal access and use of the material must be obtained from the previous owner or intermediary (e.g. culture collections) (Davis et al., 2013). GRs can also be obtained *ex situ* from readily available commodities. For example, one could culture the LAB from yoghurt or cheese and use it for commercialization of a new (probiotic) product (Zago et al., 2011). While commodities do not directly fall within the scope of the NP, utilization of GRs from these commodities does trigger benefit sharing obligations. In this case, users are expected to contact the provider country (or previous owner) and clarify whether permission for access is required and whether terms for utilization of the material need to be negotiated (European Commission, 2016).

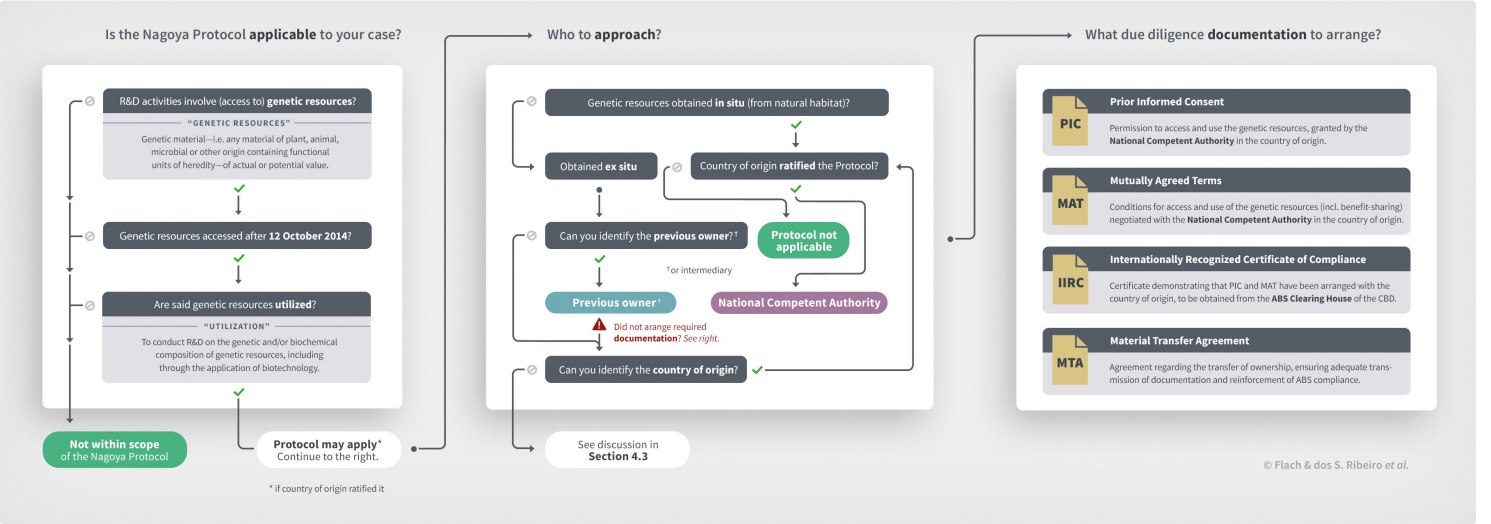

Figure 2.1 Nagoya Protocol Decision Framework.

This Figure portrays the most important considerations for companies utilizing genetic resources regarding compliance with Access and Benefit Sharing legislation. By following the steps outlined in this framework, companies can reaffirm that they have conducted the appropriate due diligence for the legal access and use of genetic resources under the Nagoya Protocol (EU Regulation 511/2014 and Implementing Regulation EU 2015/1866).

2.4.4 Due diligence requirements

Once the intended use of the GR, its origin and the applicability of the NP are determined, users must demonstrate compliance with ABS regulations by obtaining the formal certificates and agreements as described below (CBD, 2019a,b).

2.4.4.1 Prior Informed Consent (PIC)

First, users must obtain permission from the provider country to access and use the GR (if required by their national legislation). This permission is provided by the national Component Authority, usually in the form of a Prior Informed Consent certificate (PIC). The PIC details what is collected, how it is collected and by whom, what the expected use of the material will be, and describes potential emergent conditions that may require renegotiations of an existing PIC (e.g. changes in intended use). A detailed explanation of (at least) these elements should be enclosed when seeking consent. If a country grants unrestricted access to GRs, without the need of obtaining PIC, users are advised to document that no conditions were requested for access to the material according to the national regulations of the provider country.

2.4.4.2 Mutually Agreed Terms (MAT)

Subsequently, it is advisable to negotiate Mutually Agreed Terms (MAT) with the provider country´s Competent Authority, to determine conditions for access and use of the GR. A MAT certificate usually describes elements such as restriction of use, transfer to third parties, reporting requirements, and data and benefit sharing obligations. Changes in intended use, transfer, or reporting requirements may require renegotiations.

2.4.4.3 Internationally Recognized Certificate of Compliance (IRCC)

To demonstrate that users have obtained consent from the provider country (PIC) and that MAT have been established with the corresponding Competent Authority, companies are required to obtain an Internationally Recognized Certificate of Compliance (IRCC) through the ABS Clearing House on the CBD website (the platform for exchanging information on Access and Benefit-Sharing) (CBD, 2019b). A user should keep the IRCC as evidence that the GR has been accessed in accordance with the applicable regulations and transfer it to subsequent users. If GRs

are obtained *ex-situ* and there is no IRCC available, users must obtain information and relevant documents on the date and place of access, providing sources and subsequent users, characterisation of the GR, presence or absence of rights and obligations related to benefit-sharing, as well as any relevant access permits, agreements and contracts.

2.4.4.4 Material Transfer Agreement (MTA)

Finally, to reinforce compliance with benefit-sharing obligations, when stated in the MAT, a Material Transfer Agreement (MTA) should be signed for transferring the desired GR. The purpose of MTAs is to provide legal certainty regarding transfer of ownership or custodianship, and to ensure adequate transmission of associated documents (e.g. collection permits) and necessary information as required in Article 4 of the EU Regulation 511/2014 on ABS. Users are also advised to keep a record of all benefits that have been shared in relation to the GR (both monetary and non-monetary).

2.5 DISCUSSION

ABS regulations under the NP set out to promote biological diversity and sustainable use of its components by protecting the rights of indigenous and local communities. It thus remains without question that benefits need to be shared following the commercialization of GRs from traditional fermented foods or other local sources (both by users of GRs and national Competent Authorities). Nonetheless, there are various factors associated with the default implementation of the NP which make employment of the Protocol's framework and the achievement of its underlying objectives challenging (Coolsaet, 2015; Johansen, 2017).

2.5.1 Bilateral negotiations

First off, the decentralized nature of the NP gives rise to a high diversity in regulations that makes due diligence for users process-heavy and constraining, as there is a multitude of stakeholders and Competent Authorities handling these subjects at regional, national, and international levels. Governments that ratified the Protocol are impelled to define and implement legislative, administrative and policy measures on access and benefit sharing, and publish those at the ABS Clearing House on the CBD website (CBD, 2011; CBD, 2019a). These national policies differ greatly in terms of conditions and restrictive nature and therefore require cautious

research and preparation on the user's end (Buck & Hamilton, 2011; Reichman Uhlir & Dedeurwaerdere, 2016; Smith et al., 2017; Uhlir & Uhlir, 2011). Moreover, national regulations may not always be available on the Clearing House or stated in an accessible language, in which case potential users need to contact the provider country's national Focal Point (Uhlir & Uhlir, 2011). The burden of proof, however, stays with the receiving party, who will on its side be monitored by a domestic NP authority (checkpoints) and can be fined for non-compliance (Ribeiro, Koopmands & Haringhuizen, 2018). Consequently, these users may be tempted to source GRs from countries that do not exert their sovereignty rights (on the access and use of GRs) to reduce the need for multiple (time-consuming) bilateral negotiations, thereby repudiating the objectives of the CBD and leaving many GRs potentially underutilized. This may limit the flow of novel probiotic species onto the market as these are collected from a wide variety of natural sources such as plants, fruits, and animals. Other industries are feared to be affected in the same manner, such as the oncology sector where approximately 50% of all cancer drugs are natural products or directly derived there from (Newman & Cragg., 2012; Beroe, 2011)).

2.5.2 Equivocality of the Nagoya Protocol

Secondly, certain articles or definitions in the NP can be equivocal and may be challenged by ratifying parties. For instance, it remains a topic of debate whether (computerized) Genetic Sequence Data (GSD) should be considered a GR under the NP. The CBD working group on Digital Sequence Information has assessed the threats and opportunities associated with the classification of GSD under the NP (Laird & Wynberg, 2018), which fueled discussion and disagreement between signing Parties at the CBD Conference of November 2018 (Conference of the Parties 14). Similarly, there has been much debate on whether GRs originating from the human microbiome (such as LAB) should fall within the scope of the NP, as many consider these to be human GRs that should not be covered by ABS legislation (Aubertin & Filoche, 2011). Although the microbial components of the human microbiota can be used for commercial applications (such as probiotics) and are thus subject to benefit sharing; the Lactic Acid Bacteria Industrial Platform recommends that these should be specifically excluded from the NP's scope as they consider it unethical for any government to have sovereign rights over such an important element of human physiology (Laulund, 217). As people frequently travel around the world and microbes move from the human body into the environment and other hosts, this also avoids the question of ownership and nationality of a microbe. Finally, it is often debated whether high throughput screening activities

should be considered (commercial) utilization, as researchers may screen many organisms for specific properties but only utilize a few selected candidates for further development where there is a reasonable chance of commercialization. Statistically, up to 100,000 uncharacterized strains may be needed to yield one (nutri)pharmaceutical product downstream (Overmann & Scholz, 2017). Compliance certificates that need to be obtained and negotiated bilaterally for each LAB in these screening processes (for both physical bacteria and GSD) form a prominent barrier to probiotic innovation as the legislative burden is perceived disproportionally high and unattainable (Johansen, 2017; Overmann, 2015).

2.5.3 Origin of genetic resources

Lastly, many successful production systems and technologies, including LAB in yoghurt and cheese production, have been transferred to other (local) regions and nations over the years. This has led to a situation where a large share of genetic diversity used in conventional products is of exotic origin. Over time, this genetic information may have changed due to naturally occurring mutations, bilateral exchange and improvement of agricultural products and processes. It is therefore often impossible to trace the GRs from widely available commodities back to a single country of origin or to an exchange of a specific resource (Begemann et al., 2012). This makes the due diligence requirements for ABS under the NP a daunting task (section 2.4.4.4.). Moreover, LAB are GRs in food that are ready to be used and reproduced. Innovators can, and often do, culture the LAB from commodities such as yogurt or cheese, improve on it, and subsequently use it in a new (probiotic) yogurt. This completely obscures the line between providers and users of GRs, as the user will also be the provider for the next link in the chain. LAB may therefore not be understood merely as the endpoint of a development process, but rather as an intermediate step in an ongoing chain of improvements (Chiarolla et al., 2010).

2.6 RECOMMENDATIONS

As the default implementation of the NP seems to contravene the central objectives of the CBD, it is crucial that the legislative burden of the NP is alleviated and that current barriers to (probiotic) knowledge valorization are addressed. By stimulating research and development on LAB, unmet medical health needs may be abated (van den Nieuwboer., 2016a; Flach et al., 2018a) and negative perceptions towards probiotics could be improved (van den Nieuwboer et al., 2016b; Flach et al., 2017). We therefore recommend that a multilateral system (MLS) and associated treaty

are established in which conditions for access and use of LAB are agreed between all members and translated in standardized MTAs (Reichman, Uhlir & Dedeurwaerdere 2016; Ribeiro, Koopmans & Haringhuizen, 2018). This has high similarity with the Food and Agriculture Organization's (FAO) International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA) (FAO, 2009), which applies an innovative solution to ABS through its declaration that human kind's most vital crops (e.g. potatoes and rice) should comprise a pool of GRs that are accessible to everyone. Similarly, the availability of LAB is vital to the advancement of human health as they are used in the production of numerous conventional products and have an immense potential to improve disease status (Flach et al., 2018). On ratifying the proposed treaty, countries agree to make their genetic diversity and associated knowledge available to all through the MLS, where contracting Parties share a set of standardized rules of facilitated access. By facilitating research, development and information exchange with limited restrictions, costly and time-consuming efforts of users to negotiate contracts with individual parties or countries could be reduced. We also advocate that GSD and high throughput screening activities with many uncharacterized strains are exempted from ABS obligations in these agreements, at least until the moment when the few selected candidates are used for down-stream development and there is a realistic chance of commercialization (section 2.5.2). To further promote the conservation and sustainable use of biodiversity, we recommend that a complementary funding mechanism is established under the Treaty which is committed to raising funds that will endow providers and ensure their continued viability. In this sense, both monetary and non-monetary benefits strengthen the MLS. Those who access LAB through the MLS agree that they will freely share any new developments with others for further research and development through open source licenses, thereby supporting the idea of benefit-sharing, fostering the ultimate objectives of the CBD (section 2.5.3.) and conforming with the growing open-innovation practice among probiotic companies (Susanne et al., 2018; Siedlok et al., 2010). This is similar to the current system of free copyright, called "Copyleft" (Mustonen., 2003). In copyleft systems, open-source computer software can be freely used, provided that the improvements are also freely available, thereby creating a continuous chain of incrementally improved products with inherent societal value. Alternatively, if users want to keep developments to themselves, they agree to pay a percentage of commercial benefits derived from their R&D either directly to the provider country, or into a common trust fund to support conservation and sustainable use of biodiversity globally.

2.7 CONCLUSION

LAB are genetic resources for food and agriculture and as such are amenable to regulations under the ABS framework and the relevant provisions of the NP/CBD. This serves to protect the rights of indigenous and local communities and their traditional knowledge, thereby promoting conservation of biological diversity and sustainable use of its components globally. In the present study, we have developed a decision framework for companies utilizing GRs to foster these objectives and promote industry best practices. Yet, it appears that a high legislative burden combined with the multitude of local laws and regulations under the NP hampers R&D activities aimed at probiotic innovation and threatens the incentive for industrial utilization of foreign GRs. To alleviate this burden, we recommend that a multilateral system is established where standardized MTAs define the conditions for access and use of LAB between ratifying members. The use of GSD and high throughput screening activities with many uncharacterized strains should be exempted in these agreements, at least until the few selected candidates are used for downstream development, to remove a prominent barrier to probiotic innovation and support the central objectives of the CBD.

2.8 ACKNOWLEDGMENTS

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2.9 DECLARATION OF INTERESTS

E. Claassen is a consultant for several parties on probiotics, none of which are in direct conflict with the subject matter of this paper.

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